ABSTRACT

Chimeric oligonucleotide of the formula 5'–W–X^1–Y–X^2–Z–3', where W represents a 5'-O-alkyl nucleotide, each of X^1 and X^2 represents a block of seven to twelve phosphodiester-linked 2'-O-alkyl ribonucleotides, Y represents a block of five to twelve phosphorothioate-linked deoxyribonucleotides, and Z represents a blocking group effective to block nuclease activity at the 3' end of the oligonucleotide, are described. These compounds exhibit high resistance to endo- and exonucleases, high sequence specificity, and the ability to activate RNAse H, as evidenced by efficient and long-lasting suppression of target mRNA. The oligonucleotides are preferably transfected into cells in formulations containing a lipid-peptoid conjugate carrier molecule of the formula

L–linker–[$N(CH_2CH_2NH_2)CH_2(C=O)$-$N(CH_2CH_2R)CH_2(C=O)$-$N(CH_2CH_2R)CH_2(C=O)]_3$-NH_2 ,

where L is a lipid moiety, including a steroid, and each group R is independently selected from alkyl, aminoalkyl, and aralkyl.